

## Complete Summary

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### GUIDELINE TITLE

The role of isoflavones in menopausal health: consensus opinion of The North American Menopause Society.

### BIBLIOGRAPHIC SOURCE(S)

The role of isoflavones in menopausal health: consensus opinion of The North American Menopause Society . Menopause 2000 Jul-Aug; 7(4):215-29. [117 references]

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## SCOPE

### DISEASE/CONDITION(S)

Menopause

### GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness  
 Management

### CLINICAL SPECIALTY

Endocrinology  
 Geriatrics  
 Internal Medicine  
 Nutrition  
 Obstetrics and Gynecology

### INTENDED USERS

Advanced Practice Nurses  
Allied Health Personnel  
Health Care Providers  
Health Plans  
Managed Care Organizations  
Nurses  
Pharmacists  
Physician Assistants  
Physicians

#### GUIDELINE OBJECTIVE(S)

To present an evidence-based consensus opinion on the therapeutic role of isoflavones in menopausal women, either in relieving short-term symptoms or in preventing disease later in life

#### TARGET POPULATION

Perimenopausal and postmenopausal women in North America

#### INTERVENTIONS AND PRACTICES CONSIDERED

Isoflavones

1. Suggested intake amounts of isoflavones for the following conditions:

- Optimal cholesterol reduction
- Arterial compliance
- Antioxidant effect on lipids
- Bone health
- Hot flashes

Note: Specific intake amounts of isoflavones are not made for chronic diseases or for prevention of coronary artery disease or osteoporosis due to inadequate data

2. Effect of isoflavones in clinical trials for the following:

- Menopausal symptoms: hot flashes, vaginal dryness
- Cardiovascular disease: cholesterol, blood pressure, atherosclerotic plaque, arterial compliance, oxidation
- Bone metabolism
- Cognitive function
- Cancer: breast cancer, endometrial cancer, other cancers

#### MAJOR OUTCOMES CONSIDERED

Health effects of isoflavones on menopause-related symptoms and diseases related to menopause/aging

## METHODOLOGY

### METHODS USED TO COLLECT/SELECT EVIDENCE

- Hand-searches of Published Literature (Primary Sources)
- Hand-searches of Published Literature (Secondary Sources)
- Searches of Electronic Databases
- Searches of Unpublished Data

### DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The developer searched the medical literature using the database MEDLINE, and reviewed journal supplements and abstracts not on MEDLINE.

### NUMBER OF SOURCE DOCUMENTS

Not stated

### METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

### RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

### METHODS USED TO ANALYZE THE EVIDENCE

- Review
- Review of Published Meta-Analyses

### DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

### METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

### DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The North American Menopause Society (NAMS) appointed a panel of clinicians and researchers acknowledged to be experts in the field of isoflavones. Their advice was used to assist the NAMS Board of Trustees in developing this consensus opinion.

### RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

## COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

## METHOD OF GUIDELINE VALIDATION

Internal Peer Review

## DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

This Consensus Opinion was reviewed by the Board of Trustees of The North American Menopause Society.

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

#### Conclusions

The effects of isoflavones have been studied in many clinical trials, using both animal and human subjects, although the scientific rigor of some of those studies and their clinical implications have been challenged. Some data seem to be sufficient to conclude that the physiologic effects of isoflavones are beneficial, but much debate exists regarding the clinical implications of those effects.

Difficulties in obtaining definitive data include variations in response due to the populations studied, the soy products used, and the duration of exposure, as well as the nonresponse of some individuals to isoflavone or phytoestrogen supplementation. Following are conclusions drawn from an analysis of the published data on isoflavones for menopause-related conditions.

#### Menopausal symptoms

Some data support the efficacy of isoflavones in reducing the incidence and severity of hot flashes, although many studies failed to find any difference between the isoflavone recipients and the control group. Inadequate data also exist to evaluate the effect, if any, of isoflavones on vaginal dryness. Clearly, more research is needed.

#### Cardiovascular disease

It seems clear that whole soy foods are associated with favorable effects on lipid profiles. Some isoflavone supplements have shown efficacy in improving high-density lipoprotein-cholesterol and arterial compliance. In October 1999, the US Food and Drug Administration (FDA) allowed the marketing claim that 25 g/day of soy protein, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease. The FDA ruling was based on its finding that the scientific literature demonstrates a consistent, clinically significant effect of this amount of daily soy protein on total cholesterol and low-density lipoprotein-cholesterol levels.

To date, study results indicate that purified isoflavones have less effect than soy foods and soy protein on lipid levels; other components of soy seem to contribute to reducing cardiovascular disease risk factors. No studies have evaluated the effects of soy or soy components on cardiac events.

#### Bone metabolism

Although some data suggest that isoflavones may favorably affect bone health, few human studies have been conducted and all involved small numbers of subjects in trials of short duration. Future clinical studies therefore are justified in order to demonstrate whether isoflavones play a role in limiting the extent of osteoporosis.

#### Cognitive function

Few data have been published in this area. The two unpublished epidemiologic studies are conflicting in whether high consumption of one type of soy food (tofu) may have potentially harmful effects on cognitive function, whereas the limited research on animals does not suggest any adverse effects of soy, rather the possibility of improved cognitive function. Only one small study on isoflavones has been conducted.

#### Cancer

##### Breast cancer

Research has shown both protective and stimulatory effects of soy and soy isoflavones on breast cancer, based on epidemiologic, in vitro, and in vivo studies. Specific clinical trials to demonstrate a preventive action by isoflavones on breast cancer development have not been completed.

Two case-control studies show support for soy consumption in reducing breast cancer risk in premenopausal, but not postmenopausal, women. As a corollary, no evidence shows that a soy diet increases breast cancer risk in postmenopausal women.

Data obtained from studies in animals and epidemiologic studies of women living in Asia suggest that prepubertal exposure to isoflavones may be required for manifestation of breast cancer protective effects. Such information should be evaluated further before making specific recommendations that Western women increase their intake of isoflavones as a preventive measure against breast cancer.

For premenopausal women who have relatively normal ovarian function after treatment for breast cancer, opinions among experts differ on whether the modest antigonadotrophic/antigonadal actions of isoflavones would be of greater benefit than the risk of direct estrogenic stimulatory actions on undetected or new malignant cells. It has been suggested that if isoflavones, in general, and genistein, in particular, are protective against breast cancer development in vitro, then they will be beneficial to a woman who has estrogen-dependent cancers. However, it is also clear that isoflavones have estrogenic effects at certain dosage levels and at certain developmental stages of life. In a postmenopausal woman who has low-circulating estradiol levels and an estrogen-dependent tumor, dietary estrogens may stimulate tumor growth.

Some experts do not believe that food-derived isoflavones present a risk to women who have breast cancer. They believe that these isoflavones behave as selective estrogen-receptor modulators, providing specific target tissue beneficial effects. They would not discourage women who have breast cancer from consuming soy protein, because there is no conclusive evidence of untoward effects. These experts, however, do not recommend isoflavone supplements (e.g., pills) for these women, as they consider supplements to be pharmacologic agents, with the potential for overuse. Other experts believe that phytoestrogens from any source pose a risk to women who have breast cancer.

Thus, some clinicians and their patients who have estrogen-dependent tumors may have the same concerns about using isoflavones as they have about using estrogen replacement therapy. One critical difference between dietary estrogens and estrogen replacement therapy is that the dosage of estrogen replacement therapy is somewhat standardized; moreover, with isoflavones, the use typically is self-administered and not prescribed or monitored by a healthcare provider.

#### Endometrial cancer

More research is needed to clarify the relationship between soy and isoflavones and endometrial cancer.

#### Other cancers

No definitive statements can be made about the use of isoflavones and/or soy in moderating risks for other cancers found in women.

#### Isoflavone Intake Amounts

Increasing consumption of soy, soy products, and plant-based foods, in general, is supported by current recommendations to increase intake of fiber and antioxidants while lowering intake of saturated fat and cholesterol. However, it is premature to recommend specific amounts of dietary isoflavones to prevent specific chronic diseases. On the basis of the studies cited in the consensus opinion, there is some evidence, albeit limited, to suggest the following:

- Optimal cholesterol reduction seems to require approximately 50 mg/day of isoflavones; this amount would be found in approximately 25 g/day of soy protein, which corresponds to the health claim allowed by the Food and Drug Administration. There is some evidence that amounts of 40-80 mg/day of isoflavones are needed for effects on arterial compliance, and for antioxidant effect on lipids, as little as 10 mg/day may be effective. Studies are inadequate to recommend an amount to prevent coronary heart disease.
- In limited studies, a minimum of 50 mg/day of isoflavones may benefit bone health. As with coronary heart disease, there are inadequate data to recommend an amount to prevent osteoporosis.
- Most studies on hot flashes have used isoflavone amounts of 40-80 mg/day, and these amounts may benefit vasomotor symptoms.

A sizeable variation in plasma levels is seen in individuals receiving the same amount of isoflavones, an important issue as to whether a therapeutic level will be reached. Moreover, the safety of isoflavones at specific amounts has not been established. It is not clear, for example, whether the same product (e.g., a serving of isoflavone-fortified protein shake) should be consumed by a woman who has osteoporosis and a woman who has an estrogen-dependent cancer. Even

in apparently healthy women, questions exist regarding possible overuse of isoflavones.

To receive potential health benefits, it seems to be preferable to obtain isoflavones from whole foods. However, there is little quality control of food storage, time in stores, preservation, preparation, and sizes—resulting in a wide variation in the isoflavone content in foods.

Foods made from soybeans and soy-protein formulations may provide other phytochemicals that enhance the effect of isoflavones; these effects could be lost when isoflavones are given as additives alone. Isoflavone-fortified foods eventually may be an appropriate vehicle for obtaining isoflavones, although they should not be added to foods in an indiscriminate manner or on a widespread scale. The ready availability of supplements may lead the public to consume larger amounts than are advisable. If isoflavones are added to foods, they should be regulated for purity, standardization of amount, and safety.

It is unlikely that the isoflavones present in the available pills and powders all will have equivalent pharmacologic effects, as each product contains different amounts and varying concentrations. Until standardization of isoflavone extracts is achieved, it will not be possible to predict outcomes after consumption of the different supplements. In addition, the matrix in which the isoflavones are delivered will have an impact on the release of the agents for absorption and, therefore, will produce differential effects on intestinal metabolism and microflora. Like isoflavone-fortified foods, isoflavone-containing pills and powders need standardization and regulation.

Until more studies documenting benefits and safety are conducted, it is prudent for clinicians to advise their patients that whole soy foods may be a better choice than such products as supplements or soy-enriched or soy-fortified foods. Many of these products are available, and many more undoubtedly will be marketed soon, all containing differing amounts of isoflavones. When assessing patient-specific conditions, the clinician needs to be aware of this variability and to remind the patient that it is important to read labels to determine isoflavone content and to warn that, at least in the United States, there are no regulations to ensure content of such products.

### Summary

Although many studies have evaluated the effects of isoflavones, the scientific literature is conflicting because of inconsistencies in the populations studied, lack of use of an appropriate control group, selection of end points, and type of study. It is clear, however, that isoflavones may exert their actions through the estrogen receptors alpha and beta (depending on the concentration and the end-organ involved) as well as directly on enzyme systems.

Nevertheless, the role of isoflavones in the management of short-term menopausal symptoms as well as diseases related to menopause/aging is still uncertain, although there is a growing database of information suggesting that isoflavones exhibit a wide range of diverse physiologic actions in humans, including effects on menopausal symptoms, lipids and lipoproteins, vascular function, bone, and a number of cancers.

The addition of even small amounts of isoflavone-containing foods to the Western diet may reduce the risk of heart disease through beneficial effects on cholesterol levels and increased arterial compliance. Specific controlled clinical trials are needed before definitive recommendations can be made about increasing the consumption of isoflavones in large populations of women approaching menopause and beyond. However, a suggestion to eat more fruits and vegetables (specifically legumes) and less high-fat animal food is an appropriate one.

The side effects of soy may arise if soy is over consumed. Some experts argue that it might be difficult for adult women to consume sufficiently large quantities of isoflavones from traditional soy foods to cause adverse effects but that uncontrolled use of more potent isoflavone supplements might lead to negative outcomes, as estrogenic activities are dose dependent. In this regard, some level of caution needs to be maintained until more conclusive data become available.

#### CLINICAL ALGORITHM(S)

None provided

### EVIDENCE SUPPORTING THE RECOMMENDATIONS

#### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

Both published literature and clinical experience were used as a basis for the recommendations; most cited scientific research has been published in peer-reviewed journals, although some data have been published only in journal supplements or as abstracts. If the evidence was contradictory or inadequate to form a conclusion, a consensus-based opinion was made.

### BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

#### POTENTIAL BENEFITS

The most convincing health effects have been attributed to the actions of isoflavones on lipids. Studies have associated isoflavones with statistically significant reductions in low-density lipoproteins and triglycerides as well as increases in high-density lipoproteins. Although some data seem to support the efficacy of isoflavones in reducing the incidence and severity of hot flashes, many studies have not found any difference between isoflavone recipients and the controls. Inadequate data exist to evaluate the effect of isoflavones on breast and other female-related cancers, bone mass, and vaginal dryness.

Although the observed health effects in humans cannot be clearly attributed to isoflavones alone, it is clear that foods or supplements that contain isoflavones have some physiologic effects. Clinicians may wish to recommend that menopausal women consume whole foods that contain isoflavones, especially for the cardiovascular benefits of these foods; however, a level of caution needs to be observed in making these recommendations. Additional clinical trials are needed before specific recommendations can be made regarding increased consumption of foods or supplements that contain high amounts of isoflavones.



### Subgroups Most Likely to Benefit:

Women with menopause-related symptoms and/or diseases related to menopause/aging

### POTENTIAL HARMS

- Unpredictable outcomes, safety, and side effects (due to lack of standardization and regulation of isoflavone extracts)
- Inadequate data exists to evaluate the effect of isoflavones on breast cancer and other female-related cancers
- Uncontrolled use of more potent isoflavone supplements might lead to negative outcomes, as estrogenic activities are dose dependent
- The side effects associated with soy may arise if over consumed

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

Whenever possible, conclusions were drawn from scientific evidence focused specifically on isoflavones, especially trials that assessed health effects in peri- and postmenopausal women. Most clinical trials have used soy foods or isoflavones derived from soy or red clover.

Although most of the scientific research cited in the consensus opinion document was published in peer-reviewed journals, some data had been published only in a journal supplement or as an abstract. Debate exists regarding the scientific rigor of some studies, the conclusions drawn, and the clinical implications. Differing opinions of the experts are noted in the text of the document.

The scientific literature is conflicting because of inconsistencies in the populations studied, lack of use of an appropriate control group, selection of end points, and type of study.

Specific controlled clinical trials are needed before definitive recommendations can be made about increasing the consumption of isoflavones in large populations of women approaching menopause and beyond.

Two primary confounding factors when attempting to determine physiologic effects of isoflavones are (1) that many trials evaluating isoflavones fail to clarify the studied concentration of the bioavailable isoflavones, and (2) the nonspecific use of terms when reporting results from clinical studies.

The question of whether the isoflavones alone are responsible for health benefits has not been answered definitely. A considerable number of reported benefits from isoflavones are based on studies with whole soy foods: in some studies, the biologic effects of soy were lost when isoflavones were removed. Moreover, isoflavone content varied considerably among the products studied. Until standardization of isoflavone extracts is achieved, it will not be possible to predict outcomes after consumption of different supplements.

The safety of isoflavones at specific amounts has not been established. Even in apparently healthy women, questions exist regarding possible overuse of isoflavones.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Staying Healthy

### IOM DOMAIN

Effectiveness

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

The role of isoflavones in menopausal health: consensus opinion of The North American Menopause Society . Menopause 2000 Jul-Aug; 7(4):215-29. [117 references]

### ADAPTATION

Not applicable: The guideline was not adapted from another source.

### DATE RELEASED

2000 Jul

### GUIDELINE DEVELOPER(S)

The North American Menopause Society - Private Nonprofit Organization

### SOURCE(S) OF FUNDING

The consensus conference was supported by an unrestricted grant from Novogen Inc.

### GUIDELINE COMMITTEE

Expert Consensus Committee

#### COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Sadja Greenwood, MD, MPH (Chair); Stephen Barnes, PhD; Thomas B. Clarkson, DVM; John Eden, MD; W. G. Helferich, PhD; Claude Hughes, MD, PhD; Mark Messina, PhD; and Kenneth D. R. Setchell, PhD

#### FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

#### GUIDELINE STATUS

This is the current release of the guideline.

An update is not in progress at this time.

#### GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from [The North American Menopause Society \(NAMS\) Web site](#).

Print copies: Available from NAMS, P.O. Box 94527, Cleveland, OH 44101, USA (Order forms are available at [The North American Menopause Society \[NAMS\] Web site](#)).

#### AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Boggs PP, Utian WH. The North American Menopause Society develops consensus opinions. Menopause 1998 Summer; 5(2):67-8.

Electronic copies: Available from [The North American Menopause Society \(NAMS\) Web site](#).

Print copies: Available from NAMS, P.O. Box 94527, Cleveland, OH 44101, USA (Order forms are available at [The North American Menopause Society \[NAMS\] Web site](#)).

#### PATIENT RESOURCES

None available

#### NGC STATUS

This summary was completed by ECRI on January 2, 2001. It was verified by the guideline developer as of May 25, 2001.

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